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ACUTE AND CHRONIC EFFECTS OF COCAINE ON EXTINCTION-INDUCED AGGRESSION[1]

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Pigeons worked individually in a chamber containing a response key and a mirror. Pecking on the key was controlled by a multiple schedule in which a brief period of continuous food reinforcement alternated with a 5-minute period of extinction. Under baseline conditions, aggressive behavior (responding on the mirror) occurred at the onset of each extinction period. In Experiment I (acute drug administration), the aggressive behavior was decreased by doses of cocaine that had little or no effect on key pecking. Such food-reinforced responding was disrupted, however, by higher doses of cocaine. An attempt to mimic the disruptive drug effects by a prefeeding manipulation was unsuccessful. In Experiment II (chronic drug administration), some tolerance developed to the disruptive effects of cocaine on the food-reinforced responding, except at the highest dose tested. There was no clear-cut indication of tolerance to the initial effect of cocaine on the aggressive behavior at any dose.

Key words: extinction-induced aggression, cocaine, behavioral tolerance, mirror responding, key peck, pigeons

Previous research has shown that extinction following a schedule of food reinforcement will induce aggressive behavior in pigeons (Azrin, Hutchinson, and Hake, 1966; Knutson, 1970; Rilling and Caplan, 1973, 1975). Very little is known, however, about the effects of drugs on such extinction-induced aggression. In one of the few experiments in this area (Moore, Tychsen, and Thompson, 1976), the effects of chronic chlordiazepoxide administration on extinction-induced mirror responding in pigeons were assessed. It had previously been determined that responding on a mirror was functionally similar to responding on a live or stuffed target pigeon; *i.e.*, both types of responding were affected in the same way when variables in the situation (*e.g.*, the interfood interval) were manipulated (Cohen and Looney, 1973). More specifically, Moore *et al.* (1976) used a multiple schedule in which a brief period of continuous reinforcement (each key peck produced food) alternated with a 5-min period of extinction (no food). Under these baseline conditions, there was typically a burst of mirror responding at the onset of each extinction period; such responding decreased in frequency as the extinction period elapsed and never occurred during the reinforcement periods. The initial administration of chlordiazepoxide (5 mg/kg) produced a marked decrease in mirror responding, but had little or no effect on key pecking. The mirror responding generally remained suppressed during the chronic drug regimen (60 daily sessions) and returned to predrug baseline levels when the drug was withdrawn. It was concluded that the technique of extinction-induced mirror responding in pigeons provides a stable, sensitive, and recoverable baseline for objectively assessing selective drug effects on aggression.

The present research used extinction-induced mirror responding in pigeons as a baseline to study the acute and chronic effects of cocaine. Similar research using a stuffed target pigeon has recently been reported by Hutchinson, Emley, and Krasnegor (1977). Across the range of cocaine doses tested (0.03 mg/kg to 3 mg/kg), "there was a dose dependent decrease in extinction attack responses and little or no effect on CRF key peck responses. These results are consistent across the acute and chronic drug regimens" (Hutchinson *et al.*, 1977, p. 471). In that report, however, only group drug data were presented. The present research used an individual-subject approach and tested cocaine over a wider range of doses (0.01 mg/kg

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to 17 mg/kg). The objective was to provide a more complete description of cocaine's effects on extinction-induced aggression in pigeons.

EXPERIMENT I

This experiment assessed the effects of acutely administered cocaine on extinction-induced aggression.

METHOD

Subjects

Two adult male White Carneaux pigeons served; No. 4524 had been used in drug experiments involving extinction-induced mirror responding (Moore *et al.*, 1976; Polifko, 1974). The experimental history of pigeon No. 4888 involved only magazine training and shaping of the key-peck response. The pigeons were maintained within 10 g of 80% of their free-feeding weights by food presented during the sessions and by postsession supplemental feeding. The 80% values were 552 g and 520 g for No. 4524 and No. 4888 respectively. Water and grit were always available in the home cages.

Apparatus

A modified two-key pigeon chamber (BRS-Foringer PH-001) and connecting automatic control equipment were used. A detailed description of the chamber may be found elsewhere (Moore *et al.*, 1976). Briefly, the left response key on the intelligence panel could be transilluminated by either red or green light. A minimum force of about 0.2 N was required to close the microswitch behind this key. A mirror (19.8 cm by 13.4 cm), mounted on the rear wall of the chamber, was hinged along its bottom edge so that it could be displaced backwards by a blow to its surface. In the event that such a displacement exceeded a minimum force of about 0.3 N, a microswitch behind the mirror closed and a mirror response was recorded. The scheduling of events was accomplished by means of timers, steppers, and associated relay circuitry; the recording was by counters, a running-time meter, and a cumulative recorder. White noise was continuously present in the chamber to mask extraneous sounds.

Procedure

Baseline conditions. Mirror responding was induced by using a two-component multiple schedule of food reinforcement for key pecking. The components were continuous reinforcement (CRF) and extinction. During the CRF component, the keylight was green (S^D), and each of five key pecks was reinforced with food (4 sec access to mixed grain). Presentation of the food magazine was accompanied by the offset of both the keylight and the houselight and by the onset of the magazine light. The total time that the green keylight was on (S^D time) indicated the amount of pausing that occurred when food reinforcement was available. During the extinction component, the keylight was red (S^Δ), the houselight remained on, and food reinforcement was unavailable for at least 5 min. Responses made on the red key (S^Δ responses) had no effect during the first 4.5 min of extinction. However, an S^Δ response (or a mirror response) during the last 30 sec of extinction extended the component for an additional 30 sec. This delay contingency was used to prevent adventitious reinforcement (Herrnstein, 1966; Morse, 1955) of responses by the onset of the S^D. Except for the delay contingency, mirror responding had no scheduled consequences in either component. Each daily session began with the CRF component, which then alternated with the extinction component for 15 cycles. A blackout (all lights off) of variable duration (15 to 120 sec) preceded and followed each session.

Drug testing. After approximately 35 daily baseline sessions to permit stabilization (*i.e.*, no systematic change in mirror responding and S^D time across sessions), No. 4524 received nine logarithmically spaced doses of cocaine hydrochloride, ranging from 0.01 mg/kg to 17 mg/kg in mixed order, and No. 4888 received eight logarithmically spaced doses of cocaine hydrochloride, ranging from 0.01 mg/kg to 13.3 mg/kg in mixed order. The drug was dissolved in saline and injected (at a volume of 0.1 ml per 100 g body weight) into the pectoral muscle 5 min presession. On the day preceding a drug session, saline was injected intramuscularly at the same volume 5 min presession. At least three baseline sessions intervened between any drug session and the saline session that preceded the next drug session. At least two determinations for each dose were made with each pigeon.

Prefeeding probe. After the drug testing, an attempt was made to mimic the effects of the largest doses of cocaine by feeding both pi-

geons 60 g of grain 5 min presession. This amount of grain was roughly four times the amount ordinarily required each day to maintain the subjects' body weights within 10 g of 80% of their free-feeding weights. Two determinations for this prefeeding probe, spaced about three days apart, were made with each pigeon.

Results

Figure 1 shows a summary of the effects of varying doses of cocaine on the mirror responses and S^D time per session for both pigeons. The drug was considered to have an effect to the extent that the data points fell outside of the ranges for the saline (S) sessions. As can be seen, cocaine decreased mirror responding at doses above 1 mg/kg in both pigeons. Doses below 1 mg/kg had no effect on the mirror responding of either bird. Aside from two slight decreases (No. 4888; 1 mg/kg and 5.6 mg/kg), S^D time was unaffected by all doses of cocaine below 10 mg/kg in both pigeons. Doses above 10 mg/kg produced large increases in S^D time in both subjects (note log scale on y-axis). These results show that cocaine had a selective effect on mirror responding; *i.e.*, mirror responding was decreased by doses of the drug that had little or no effect on S^D time (No. 4524, 1 mg/kg through 10 mg/kg; No. 4888, 3 mg/kg and 5.6 mg/kg).

Figure 2 shows some cumulative records of the within-session mirror responding of No. 4524 throughout this experiment. During the saline sessions, although the amount of mirror responding varied somewhat from cycle to

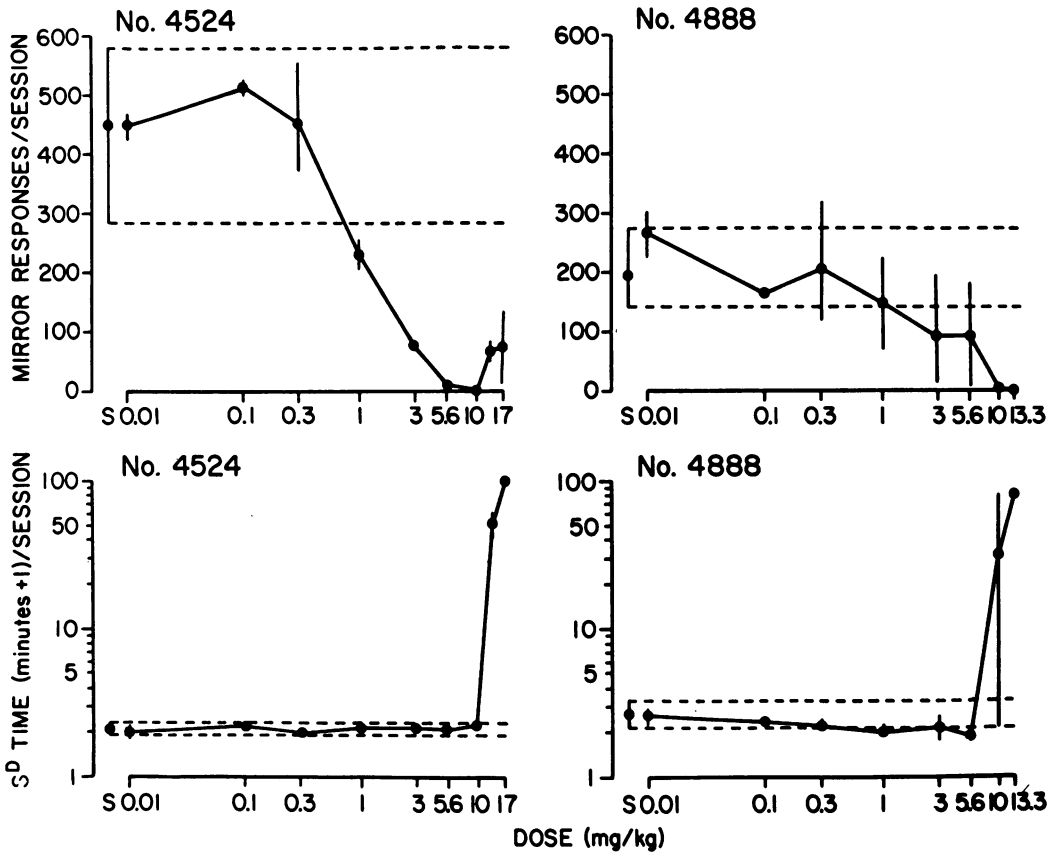

Fig. 1. Effects of acute cocaine administration on the mirror responses and S^D time of two pigeons (No. 4524 and No. 4888) under a multiple CRF-extinction schedule of food reinforcement for key pecking. Each point on each dose-response curve represents the mean of all determinations at a particular dose; the vertical lines through the points on the curve indicate the range. The two dashed horizontal lines for each behavioral measure indicate the control range of variability (saline sessions). The points situated along the vertical lines demarking the control ranges indicate the mean value of saline-control responding for each measure. A constant (1 min) was added to each S^D time to facilitate the plotting of the data on a logarithmic scale.

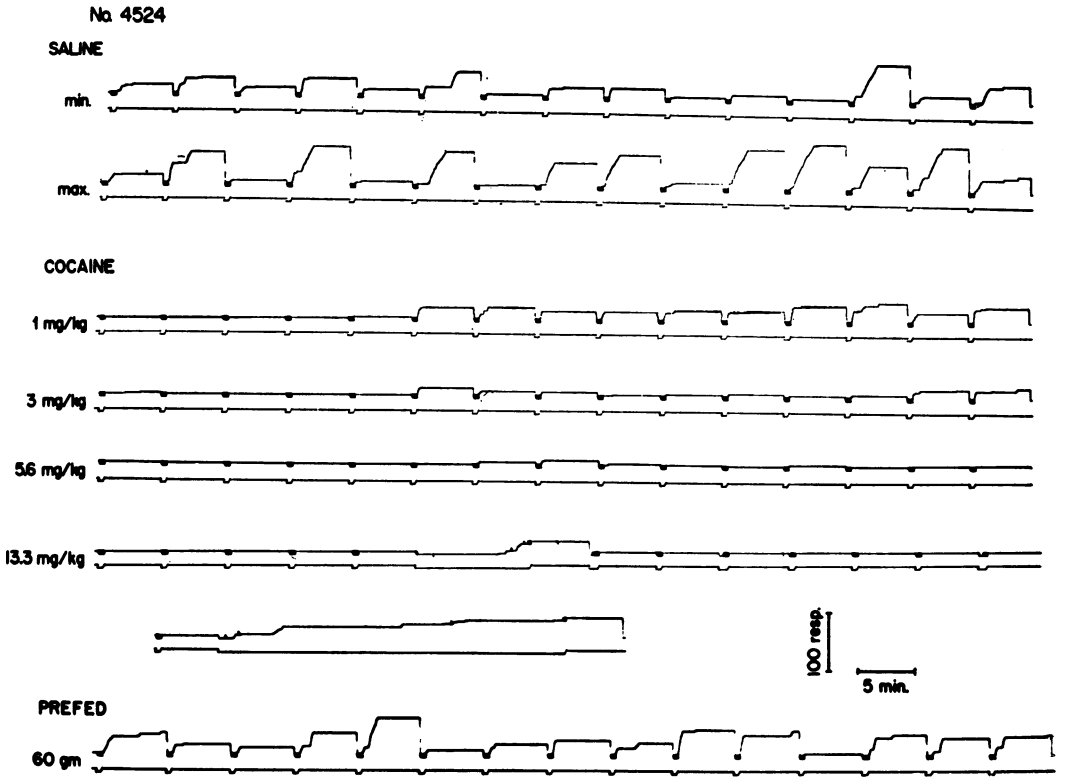

Fig. 2. Cumulative response records showing the within-session effects of acutely administered cocaine and presession feeding on the mirror responding and S^D time of No. 4524 (first determinations). The saline sessions with the minimum and maximum number of mirror responses are also shown. The response pen, which traced the top line of each pair, stepped upward with each mirror response and reset at the end of each extinction component. A downward deflection of the response pen during extinction indicates a key peck (S^Δ response). During the CRF component, the response pen deflected upward with each of the five reinforced key pecks, producing the dark segments seen on the records (S^D time). The event pen, which traced the bottom line of each pair, was held down during the CRF components.

cycle of the multiple schedule, the temporal pattern of mirror responding was consistent in that (1) mirror responding generally occurred at the onset of each extinction component, (2) almost all mirror responding occurred during the first half of each extinction component, and (3) mirror responding did not occur during any of the CRF components. Acute administration of 1 mg/kg, 3 mg/kg, and 5.6 mg/kg of cocaine produced dose-related decreases in mirror responding. However, these same doses had no effect on S^D time (pausing during the CRF component), as can be seen from the unchanged width of the displacements of the event pen. Note that at these three doses of cocaine, when mirror responding did occur, its temporal pattern was unaltered by the drug. Administration of 13.3 mg/kg of cocaine to this subject produced decreases in mirror responding associated with large increases in S^D time. In Cycles 6 and 15, the pigeon took well over 5 min in each case to complete the five reinforced key pecks, and in the pauses between key pecks, mirror responding occurred. Comparison of the records for 3 mg/kg and 13.3 mg/kg emphasizes the difference in the temporal pattern of mirror responding at these widely separated doses. It is important to note, however, that the total amount of mirror responding at these two doses is very similar (see Figure 1, top left, 3 mg/kg and 13.3 mg/kg), suggesting that analysis of data solely in terms of session totals may be misleading. The results obtained from the prefeeding probe were unambiguous. A representative session (see Figure 2, bottom), before which No. 4524 was fed 60 g of grain, shows that this manipulation produced no noticeable change in mirror responding or S^D time. In all respects, the within-session data of

No. 4888 (not shown) were similar to those of No. 4524, except that when cocaine-induced pausing occurred in No. 4888, it was typically restricted to the first cycle of the session, before the first reinforced key peck.

EXPERIMENT II

This experiment assessed the effects of chronically administered cocaine on extinction-induced aggression.

METHOD

Subjects

The subjects were the same two pigeons that served in Experiment I.

Apparatus

The apparatus in Experiment I was used.

Procedure

Baseline conditions. The baseline conditions were the same as those in Experiment I.

Drug testing. After 15 to 25 daily baseline sessions to permit stabilization (*i.e.,* no systematic change in mirror responding and S^D time across sessions), there were 10 daily control sessions in which saline was injected intramuscularly 5 min presession. The volume of each injection was 0.1 ml per 100 g body weight. Immediately following the last of these control sessions, a chronic cocaine regimen was instituted as follows. Both birds initially received 1 mg/kg/day for 90 consecutive days. This dose of cocaine was selected as a starting point for the chronic study because it was the lowest dose administered during the acute testing (Experiment I) that produced a selective effect in both pigeons (see Figure 1, top left, bottom right). No. 4524 then received 10 mg/kg/day of cocaine for 60 consecutive days, after which the baseline conditions were reinstated for 15 days. Following the 1 mg/kg/day regimen of cocaine, No. 4888 received 10 mg/kg/day for 40 consecutive days, then 13.3 mg/kg/day for 30 consecutive days, after which the baseline conditions were reinstated for 15 days. All doses of cocaine hydrochloride were dissolved in saline and injected (at a volume of 0.1 ml per 100 g body weight) into the pectoral muscle 5 min presession.

RESULTS

Figure 3 shows a session-by-session summary of the effects of repeated administration of cocaine on the mirror responses and S^D time of No. 4524. The drug was considered to have an effect to the extent that the data points fell outside of the saline-control ranges. Initial administration of 1 mg/kg of cocaine to this pigeon decreased mirror responding and increased S^D time. During repeated administration of this dose, mirror responding was quite variable, although an increasing trend was evident. After the initial small increase in S^D time produced by 1 mg/kg of cocaine, this measure was affected little, if any, by subsequent administration of this dose. Initial administration of 10 mg/kg of cocaine to No. 4524 produced a marked decrease in mirror responding and a large increase in S^D time. During subsequent exposure to 10 mg/kg/day of cocaine, mirror responding generally remained well below the saline-control values, whereas S^D time showed a decreasing trend toward control as the drug regimen continued. Thus, with repeated administration of 10 mg/kg of cocaine to No. 4524, partial tolerance to cocaine's disruptive effect on food-reinforced responding (S^D time) was obtained. Both mirror responding and S^D time returned to control values during the postdrug baseline period.

Figure 4 shows cumulative records of No. 4524 for the first and last sessions at 10 mg/kg/day and for the final postdrug baseline session. Initial administration of 10 mg/kg of cocaine clearly reduced mirror responding to near-zero levels throughout the session. The increase in S^D time produced by the initial administration of this dose of cocaine (see Figure 3, bottom, Session 91) is seen on the cumulative record as a long pause preceding the first reinforced key peck of the session. After 60 days of treatment with 10 mg/kg/day of cocaine, this initial pause was attenuated considerably; *i.e.,* partial tolerance developed to cocaine's disruptive effect on food-reinforced responding. Furthermore, despite the fact that mirror responding did reappear during many sessions at 10 mg/kg/day of cocaine (see Figure 3, top, Sessions 105 to 120), its temporal pattern was similar to that shown in the middle record of Figure 4 (10 mg/kg, Day 60); mirror responding seldom occurred immediately after the onset of extinction, and it often occurred during the last half of the extinction period. Recovery of predrug baseline performance is

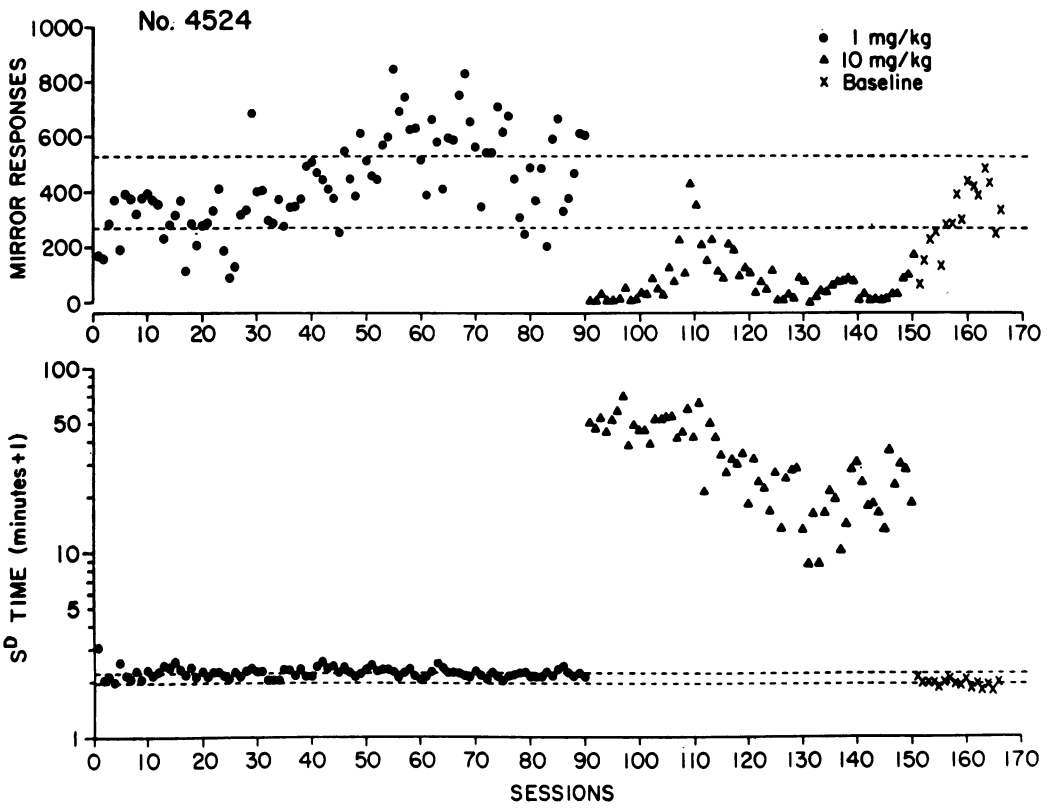

Fig. 3. Effects of chronic cocaine administration on the mirror responses and S^D time of No. 4524 under a multiple CRF-extinction schedule of food reinforcement for key pecking. The two dashed horizontal lines for each behavioral measure indicate the control range of variability, which was based on 10 predrug saline sessions.

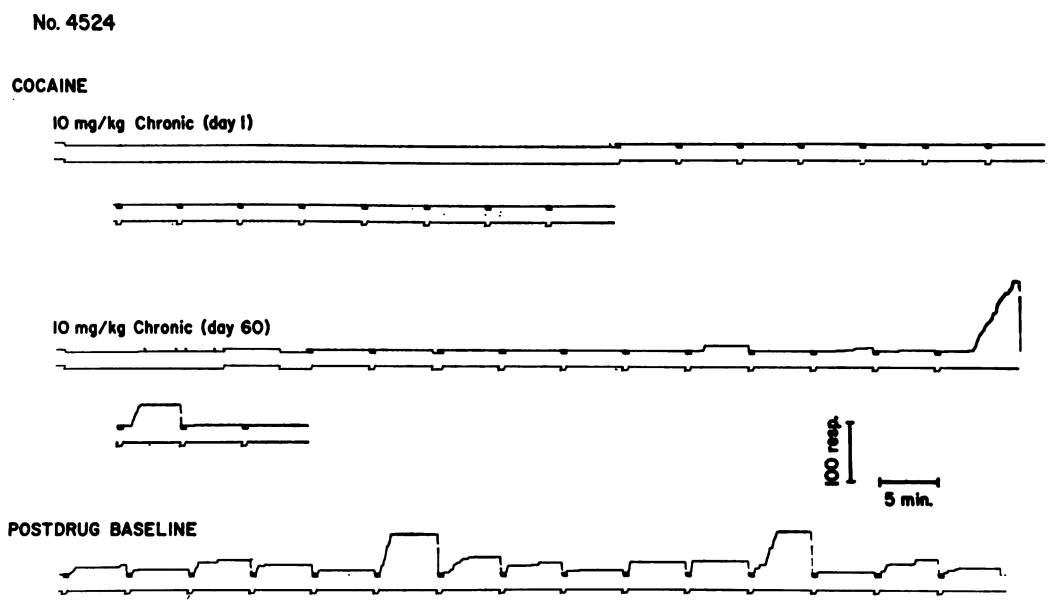

Fig. 4. Cumulative response records of No. 4524 for the first and last chronic cocaine sessions at 10 mg/kg/day and for the final postdrug baseline session. The recording details are the same as in Figure 2.

illustrated in the bottom record of Figure 4 (compare this record with the saline sessions in Figure 2).

A session-by-session summary of the performance of No. 4888 during the chronic cocaine regimen is shown in Figure 5. Initial administration of 1 mg/kg of cocaine to this subject had no effect on mirror responding; S^D time was decreased slightly, as it had been during the acute testing when this dose was given (see Figure 1, bottom right, 1 mg/kg). Repeated administration of 1 mg/kg of cocaine to this bird tended to decrease levels of mirror responding after about 50 sessions. Note, however, that the majority of the data points at this dose fell within the saline-control range. The slight decrease in S^D time produced by the initial administration of 1 mg/kg of cocaine to this subject was a sustained effect; tolerance failed to develop to this action of the drug with repeated administration at this dose. Initial administration of 10 mg/kg of cocaine to No. 4888 decreased mirror responding to near-zero levels. This decrease was associated with a large increase in S^D time. During repeated administration of the 10 mg/kg dose to this subject, mirror responding remained at very low levels, whereas S^D time tended to decrease until it fell within the saline-control range. Increasing the dose to 13.3 mg/kg/day of cocaine for No. 4888 produced more variable S^D times, which were generally above the control range; the mirror responding remained at near-zero levels. Both mirror responding and S^D time returned to control values during the postdrug baseline period.

A comparison of the acute and chronic (Day 1) effects of two doses of cocaine (10 mg/kg and 13.3 mg/kg) on the mirror responding and S^D time of No. 4888 is illustrated in the cumulative records of Figure 6. Taken together, the first two cumulative records demonstrate that previous exposure of No. 4888 to 90 consecutive days of 1 mg/kg/day of cocaine had little influence on the way this subject was affected by the initial 10 mg/kg chronic dose. Mirror responding decreased to

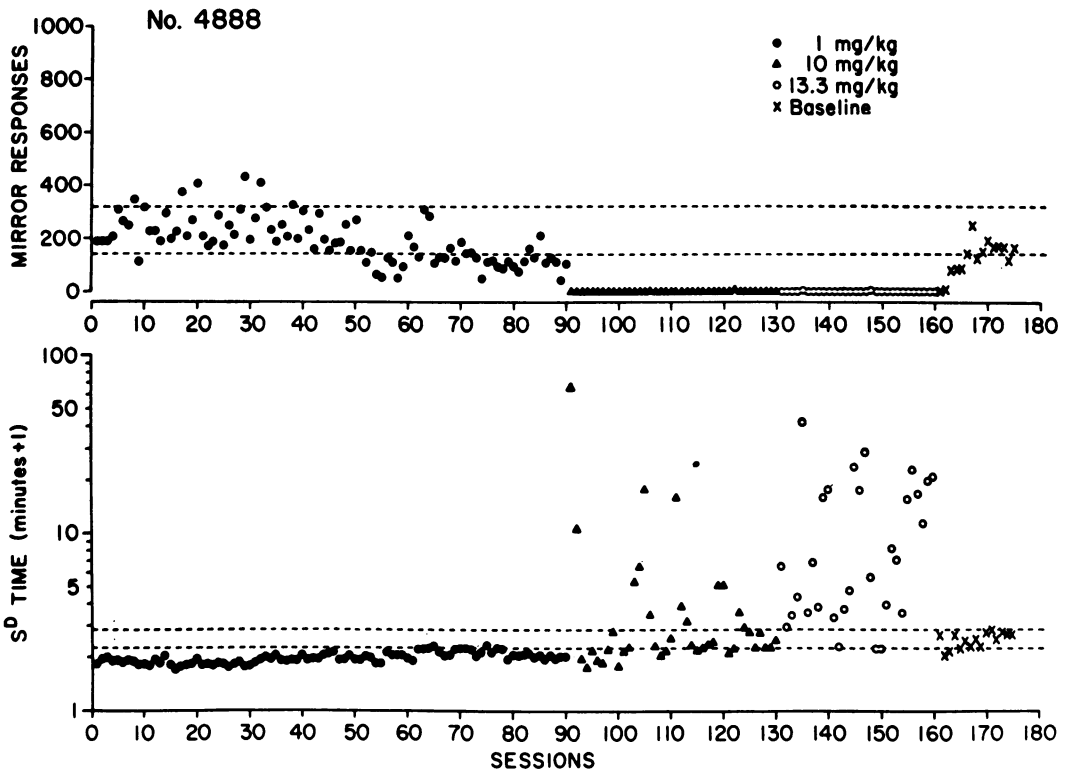

Fig. 5. Effects of chronic cocaine administration on the mirror responses and S^D time of No. 4888 under a multiple CRF-extinction schedule of food reinforcement for key pecking. The two dashed horizontal lines for each behavioral measure indicate the control range of variability, which was based on 10 predrug saline sessions.

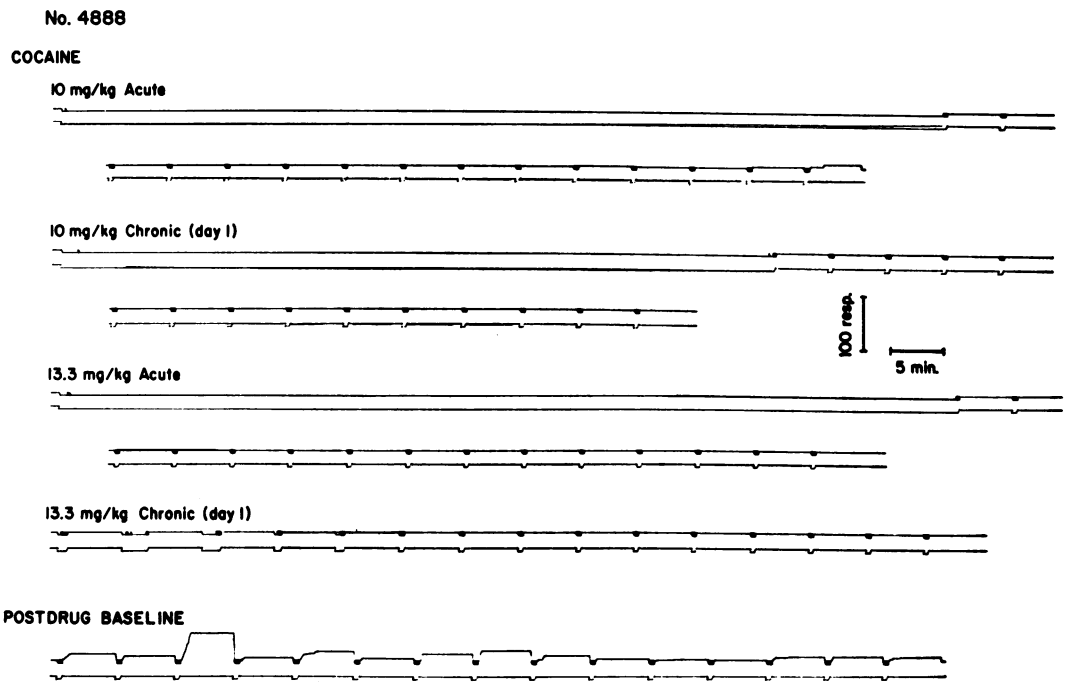

Fig. 6. Cumulative response records of No. 4888 comparing acute and chronic (Day 1) cocaine effects at two doses. Both acute drug sessions are from the last determinations at each dose; *i.e.*, they represent the acute tests closest in time to the chronic (Day 1) tests. The response record for the final postdrug baseline session is also shown. The recording details are the same as in Figure 2.

similar low levels in both cases, although the initial pause during CRF was somewhat longer when 10 mg/kg was tested in the acute phase of the study. In contrast, the next pair of cumulative records shows that previous exposure of No. 4888 to 40 consecutive days of 10 mg/kg/day of cocaine markedly decreased the initial pause at 13.3 mg/kg. Stated another way, the dose-effect relation for S^D time in this subject appears to be "shifted to the right" (a given dose produces a smaller effect) by prior exposure to a chronic high-dose cocaine regimen. Recovery of predrug baseline performance is shown in the bottom cumulative record of Figure 6. The amount and temporal pattern of mirror responding returned to control, as did the S^D time measure.

GENERAL DISCUSSION

In the acute phase of the present research, extinction-induced mirror responding was decreased by doses of cocaine (3 mg/kg and 5.6 mg/kg) that had little or no effect on food-reinforced key pecking (Figures 1 and 2). Similar selective effects have been obtained with a variety of drugs in studies employing schedule-induced attack in pigeons as a behavioral baseline. Cherek and Thompson (1973) reported that Δ^9-tetrahydrocannabinol selectively decreased attack responding on both live and stuffed targets when administered acutely (0.25 mg/kg) to pigeons working under a fixed-interval schedule of food reinforcement. Polifko (1974) found that acute administration of pentobarbital (10 mg/kg) and phenobarbital (40 mg/kg) to pigeons working under a multiple CRF-extinction schedule decreased attack responding on a mirror without affecting food-reinforced key pecking. A recent study from this laboratory demonstrated the selective anti-aggressive effect of chlordiazepoxide (5 mg/kg) in pigeons working under a multiple CRF-extinction schedule of food delivery (Moore *et al.*, 1976). It is quite possible, of course, that with different schedule parameters, differential effects between the drugs could be detected. Similarly, the selective effect of a given drug may also depend on the schedule of reinforcement used. For example, if key pecking had been reinforced on a large fixed-ratio schedule, instead of CRF, then

such responding might have been affected by lower doses of cocaine, perhaps even by doses that did not affect mirror responding.

In the above studies, increasing the dose of the drug generally produced a breakdown in the selectivity of its action on attack responding; *i.e.,* some dose of each drug was found that also affected food-maintained responding. Increasing the dose of cocaine administered in the present study had the same consequence; at doses above 10 mg/kg, marked disruption of food-reinforced responding was obtained in both pigeons (Figure 1). Hutchinson *et al.* (1977), in their study of the effects of cocaine on extinction-induced aggression in pigeons, did not obtain a similar dose-related breakdown in the selectivity of the drug's effect on aggressive behavior. These investigators reported that acute administration of the drug (intramuscularly, 30 min presession) in doses ranging from 0.03 mg/kg to 3 mg/kg produced decreases in attack responding on a stuffed target pigeon without affecting food-maintained key pecking. The present results suggest that the selective cocaine effect obtained in the Hutchinson *et al.* (1977) study is a dose-dependent phenomenon and, had those investigators increased the dose of cocaine further, disruptive effects on food-maintained behavior would have become apparent.

Generally, cocaine-induced disruption of key pecking maintained by continuous food reinforcement in the present study took the form of a long pause before the first reinforced key peck of the session (*e.g.,* Figure 4, 10 mg/kg Chronic, Day 1; Figure 6, 13.3 mg/kg Acute). These long pauses are a characteristic effect of cocaine on operant responding under a wide variety of circumstances, *e.g.,* pigeons working under fixed-ratio schedules of food reinforcement (McMillan, Dearstyne, and Engstrom, 1975; Thompson, *in press a*), rats working under fixed-ratio schedules of food (Pickens and Thompson, 1968) or water (MacPhail and Seiden, 1975) reinforcement, as well as in monkeys working under fixed-ratio (Gonzalez and Goldberg, 1977; Wilson and Schuster, 1975; Woods and Tessel, 1974) or DRL (Morrow and Ferraro, 1976) schedules of food reinforcement. The possibility that cocaine may produce its disruptive effect on food-reinforced responding via a "selective anorexic" action has been put forth by Wilson and Schuster (1975). In this regard, Dews (1956) suggested that if a drug affects food-reinforced responding by modifying the deprivation conditions ("hunger", "appetite", *etc.*), then the effect of the drug should be mimicked by manipulation of the deprivation conditions by other means. This was the rationale for the prefeeding probe that followed drug testing in the present experiment. However, feeding the pigeons 60 g of grain before the start of a session failed to affect food-reinforced responding during the session (*e.g.,* Figure 2, last record). The possibility remains that the high-dose cocaine effect could have been mimicked if the pigeons had been fed even more, but this seems improbable considering that both birds actually stopped eating before the entire 60 g of grain were consumed (2 to 5 g of the 60 g remained in the food trays when the pigeons stopped eating). Thus, it seems unlikely that an "anorexic" action of cocaine was responsible for the disruptive effects obtained on food-maintained behavior in the present research.

At high doses of cocaine, mirror responding occasionally occurred during the long pauses in food-reinforced responding (*e.g.,* Figure 2, 13.3 mg/kg). Such intrusion of responses normally associated only with the extinction component of the multiple schedule into the CRF component may be interpreted as evidence of a breakdown in stimulus control. Similar instances of drug-induced loss of stimulus control of responding under various multiple schedules have been reported (see review by Thompson, *in press b*).

The present study demonstrated the development of behavioral tolerance to certain of the effects of cocaine during repeated administration of the drug. The tolerance observed was generally consistent with the hypothesis introduced by Schuster, Dockens, and Woods (1966) to explain the diminished behavioral effect of repeated amphetamine administration. More specifically, these investigators proposed that, "behavioral tolerance will develop in those aspects of the organism's behavioral repertoire where the action of the drug is such that it disrupts the organism's behavior in meeting the environmental requirement for reinforcements. Conversely, where the actions of the drug enhance or do not affect the organism's behavior in meeting reinforcement requirements we do not expect the development of behavioral tolerance" (Schuster *et al.,* 1966, p. 181). At doses of 1 mg/kg and 10 mg/kg, if

cocaine initially increased S^D time (*i.e.*, decreased the rate of reinforcement), then the drug had a diminished effect with repeated administration (No. 4524, 1 mg/kg and 10 mg/kg; No. 4888, 10 mg/kg). If, however, cocaine initially increased the rate of reinforcement, then tolerance failed to develop during chronic administration (No. 4888, 1 mg/kg). Since mirror responding did not affect the rate of reinforcement, tolerance would not be expected to develop to any effect of cocaine on mirror responding. The present results revealed no clear-cut indication of tolerance to the initial effect of cocaine on mirror responding at any dose (Figures 3 and 5). Noteworthy in the present study is the finding that, although 13.3 mg/kg of cocaine initially decreased the rate of reinforcement of No. 4888, tolerance failed to develop to this disruptive effect of the drug with repeated administration (see S^D time in Figure 5). This finding suggests that the hypothesis of Schuster *et al.* (1966) may not apply when relatively large doses of drugs are chronically administered (*cf.* Thompson, 1974).

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